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Local Radiotherapy Affects Drug Pharmacokinetics—Exploration of a Neglected but Significant Uncertainty of Cancer Therapy

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Abstract

Purpose: Concurrent chemoradiation therapy is the mainstay of treatment for many types of malignancies. However, concurrent chemoradiation therapy is associated with a greater number of systemic adverse effects than radiotherapy or chemotherapy alone. **Summary:** Pharmacokinetics is the study of a drug and/or its metabolite kinetics in the body, including absorption, distribution, metabolism, and elimination. The incidences of adverse effects are markedly higher in patients who receive concurrent chemoradiation therapy than in those who receive either radiotherapy or chemotherapy alone. This phenomenon implies that irradiation affects the pharmacokinetics of cytotoxic agents, namely the radiotherapy–pharmacokinetic phenomenon. Experimental animal studies have shown that local irradiation affects the systemic pharmacokinetics of 5-fluorouracil and cisplatin at both low dose (simulating generous dose distributed to normal tissues) and daily practice dose (mimicking therapeutic dose to target volumes). These effects are significant in the circulation of blood and lymphatic system as well as in the hepatobiliary excretion. Furthermore, recent studies have demonstrated that matrix metalloproteinase-8 plays an important role in the radiotherapy–pharmacokinetic phenomenon. **Conclusion:** In the present review, we provide a general overview of the radiotherapy–pharmacokinetic phenomenon and discuss the possible mechanisms governing the phenomenon.

Keywords

concurrent chemoradiation therapy, pharmacokinetics, RT-PK phenomenon, radiotherapy, uncertainty

Abbreviations

3DCRT, 3-dimensional conformal radiotherapy; 5-FU, 5-fluorouracil; 5-FDH2, 5-fluoro-5,6-dihydro-uracil; AUC, area under the curve; CCRT, concurrent chemoradiation therapy; CDDP, cisplatin; DPD, dihydropyrimidine dehydrogenase; ESTRO, European Society for Radiotherapy and Oncology; GI, gastrointestinal; IL-6, interleukin 6; IMRT, intensity-modulated radiotherapy; JNK, c-Jun NH2-terminal kinase; MAPK, mitogen-activated protein kinase; MMP-8, matrix metalloproteinase-8; PI3 K, phosphatidylinositol (PtdIns) 3-kinases; PMNs, polymorphonuclear neutrophils; PIP3, PtdIns(3,4,5)P3; PK, pharmacokinetics; PVI, protracted venous infusion; RT-PK, radiotherapy–pharmacokinetic; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α.

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Background

Concurrent chemoradiation therapy (CCRT) comprises the administration of cytotoxic agents in conjunction with radiation therapy as treatment for advanced stage cancer. Cisplatin (CDDP) and 5-fluorouracil (5-FU) are the most commonly used cytotoxic agents in CCRT and are known to increase the relative radiosensitivity and radiosensitization of hypoxic cells,[1,2] synchronize and redistribute tumor cells in cell cycle G2 and M phases,[3,4] kill S phase cells,[5] inhibit repair of DNA double-strand breaks,[6] suppress tumor neovascularization,[7] and strengthen the killing effect of radiation.[8-10] Chemotherapeutic regimens that named as metronomic regimens are delivering the chemotherapeutic drugs with the low, less toxic doses, prolonged periods of time, and no extended drug-free breaks by close regular administration.[11-13] The main targets of metronomic chemotherapy are the endothelial cells of the growing vasculature of a tumor.[11,14] These characteristics of CDDP and 5-FU as radiosensitizers contribute to the improved locoregional control and survival rates in patients with locally advanced cancer.[15-23]

However, the incidence of adverse effects such as hematologic, gastrointestinal (GI), and severe acute toxicities is markedly higher in patients who receive CCRT with 5-FU- or CDDP-base regimen than in those who receive either radiotherapy or chemotherapy alone, no matter of neoadjuvant setting, definitive setting, or adjuvant setting.[15,16,18,21-29] Pharmacokinetics (PK) is the study of kinetics of absorption, distribution, metabolism, and excretion of drugs and their corresponding pharmacologic, therapeutic, or toxic responses in man and animals.[30] Absorption is defined as the process by which a drug proceeds from the site of administration to the site of measurement (usually blood, plasma, or serum). Distribution is the process of reversible transfer of drug to and from the site of measurement (usually blood or plasma). Metabolism is the process of a conversion of one chemical species to another chemical species. Excretion is defined as the irreversible loss of a drug in a chemically unchanged or unaltered form.[30]

The combinations of certain drugs can mimic, increase, or reduce the effects of one or all components, resulting in clinically important interactions that was proven by PK parameters.[31-33] For example, St-John's-wort (*Hypericum perforatum*) reduces the plasma concentrations (and/or increases the clearance) of digoxin, theophylline, cyclosporin, and phenprocoumon via cytochrome P450 and/or P-glycoprotein.[34,35] Case series also suggest interactions of St-John's-wort with adrenergic vasopressors, anesthetics, bupropion, cyclosporin, nevirapine, oral contraceptives, paroxetine, phenprocoumon, prednisone, sertraline, tacrolimus, theophylline, warfarin, and so on.[31,36,37] Clinical cases indicate interactions of ginkgo (*Ginkgo biloba*) with antiepileptics, aspirin (acetylsalicylic acid), diuretics, ibuprofen, risperidone, rofecoxib, trazodone, and warfarin.[38-40] Moreover, soluble fibers (including guar gum and psyllium) can decrease the absorption of drugs.[37] Pharmacokinetic variables can be affected by organ-based changes following irradiation, resulting in change in treatment response or adverse effects.[41,42] Blackstock et al noted the tumor retention of 5-FU was prolonged in animals receiving radiation before the drug infusion, and the tumor clearance rate of the 5-FU was a 3-fold reduction in the irradiated tumors.[41] Schlemmer et al also noted the 5-FU levels were significantly higher after CCRT when compared with the first chemotherapy delivering.[42] A number of animal studies have shown that local irradiation affects the systemic PKs of 5-FU and CDDP regardless of the dose.[43-46]

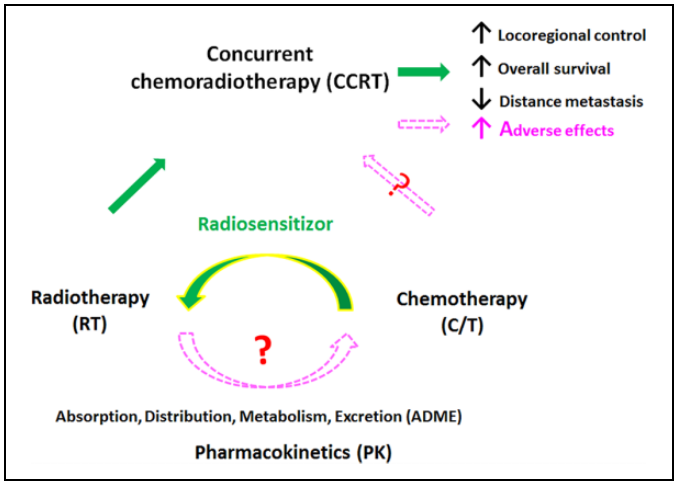

Figure 1. A diagram showing how irradiation might modulate the pharmacokinetics of anticancer drugs. The dotted line arrow indicates uncertainty. C/T indicates chemotherapy; CCRT, concurrent chemoradiation therapy; PK, pharmacokinetics; RT, Radiotherapy.

Advanced radiotherapy modalities such as 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), helical tomotherapy, and arc radiotherapy allow for the precise delivery of radiation doses to the tumor while sparing critical organs.[47-50] Nonetheless, each modality results in a general, low-dose distribution of radiation to the torso.[43] Coppes and colleagues found that the out-of-field effects of radiation on vascular damage were very similar to the in-field effects.[51] Erpolat et al found that IMRT planning resulted in lower irradiated bone marrow volumes than 3DCRT planning.[52]

These phenomena imply that irradiation affects the PK of cytotoxic agents and is referred to as the radiotherapy–pharmacokinetic (RT-PK) phenomenon. On the other hand, much less is understood about the biological effects of this phenomenon, especially when advanced, conformal radiation techniques with low-dose distribution are used (Figure 1). In this review, we provide a general overview of the RT-PK phenomenon and discuss the possible mechanisms governing the phenomenon.

Search Methods for Identification of Studies

The medical databases listed below were searched for English publications from their inception to July 2017.

PubMed (https://www-ncbi-nlm-nih-gov.lib.ym.edu.tw/pubmed/),
MEDLINE (https://www.medline.com/),
ClinicalKey (https://www-clinicalkey-com.lib.ym.edu.tw/), and
Cochrane Library (http://www.cochranelibrary.com.lib.ym.edu.tw/).

Electronic database searches were performed with MeSH terms and free text terms.

For MeSH terms searching, (1) ("Pharmacokinetics"[Mesh] AND "Radiotherapy"[Mesh]) AND "Neoplasms"[Mesh]) OR "Cisplatin"[Mesh]) OR "Fluorouracil"[Mesh]) AND "Rectal Neoplasms"[Mesh]) OR "Uterine Cervical Neoplasms"[Mesh]) AND "Chemoradiotherapy"[Mesh] AND ("2007/09/06"[PDAT]: "2017/09/02"[PDAT]) AND (Clinical Trial[ptyp] AND "2007/09/06"[PDAT]: "2017/09/02"[PDAT] AND English[lang]) were used, and the numbers of article were 254; (2) ("mitogen-activated protein kinase kinases"[Mesh] OR "Phosphatidylinositol 3-Kinases"[Mesh]) AND "Radiotherapy"[Mesh] were used, and the numbers of article are 56; (3) "Bystander Effect"[Mesh] AND "Radiotherapy"[Mesh] were used, and the numbers of article are 89.

For free text terms searching, we used abscopal effects, bystander effects, irradiation, chemotherapy, concurrent chemoradiation, combined modality, metronomics, PKs, radiotherapy, radiochemotherapy, radiosensitization, rectal neoplasm, and uterine cervical neoplasms. For manual search/abstract search, we searched *Cancer*, *Cancer Letter, Cancer Research, Lancet, Journal of Clinical Oncology, International Journal of Radiation Oncology Biology Physics, Radiotheraphy Oncology, New England Journal of Medicine, Nature Review Clinical Oncology*. Proceedings were searched from American Society for Radiation Oncology, European Society for Radiotherapy & Oncology, and American Society of Clinical Oncology.

Literature Selection

Unpublished data, case reports, letters, editorials, and comments were excluded from the analysis. Multiple articles published by the same author over a short period were also excluded.

The RT-PK Phenomenon

The RT-PK Phenomenon of 5-FU

In plasma. 5-Fluorouracil increases the radiosensitivity of RT and is metabolized in the liver via a catabolic pathway and an anabolic pathway.[5,53-56] The liver catabolyzes about 80% of 5-FU via the dihydropyrimidine dehydrogenase (DPD) pathway to generate toxic 5-fluoro-5,6-dihydro-uracil (5-FDH2), and DPD is a rate-limiting step.[55,56] In the anabolic pathway, 5-FU via orotate phosphoribosyl transferase produces active metabolites including 5-fluorouridine-5′-monophosphate, 5-fluorouridine, and 5-fluoro-2′-deoxyuridine.[53,54]

Concurrent chemoradiation therapy has been shown to result in better pathological response and local control in rectal cancer than RT alone but that the incidence of grade 3 or 4 toxicity is significantly higher after CCRT (15%-29%) than after RT (0%-6%), no matter of neoadjuvant setting,[24,25] definitive setting,[15,16] or adjuvant setting.[26] In the meta-analysis of head and neck cancer studies, RT combined with 5-FU or CDDP as a single drug or 5-FU-base chemotherapeutic agents resulted in a large survival advantage.[19,20] However, CCRT is also associated with high rates of hematologic toxicity and other systemic adverse effects in head and neck cancer treatment.[57,58]

The PK of 5-FU can be used to predict disease recurrence.[59,60] Di Paolo and Lencioni found that the area under the curve (AUC) of 5-FU was significantly lower in patients with colorectal cancer with recurrent disease than in patients without disease recurrence.[59] In addition, Milano et al reported that patients with longer 5-FU systemic exposure had longer disease-free survival.[60] In 3 previous studies, we explored the effects of low-dose radiotherapy and practical dose radiotherapy on anticancer drugs in rats. Animals were randomized to receive 0 Gy (control), 0.5 Gy (representing a dose deposited in the off-target area in clinical practice), or 2 Gy and then were administered 5-FU following RT to check the RT-PK phenomena of anticancer drugs.[43-46,61]

Intriguingly, whole abdominal irradiation resulted in a 21% reduction in the AUC of 5-FU at 0.5 Gy and a reduction of 32% at 2 Gy.[43] Similarly, pelvic irradiation (excluding the liver and kidneys) resulted in an 18% reduction in the AUC of 5-FU at 0.5 Gy and a 22% reduction at 2 Gy. In bile, there was a 25% increase in the AUC of 5-FU at 0.5 Gy and a 31% increase at 2 Gy.[44] Also, head and neck irradiation significantly reduced the AUC of 5-FU by 17% at 0.5 Gy and by 16% at 2 Gy. In bile, the AUC of 5-FU increased by 12% at 0.5 Gy and by 25% at 2 Gy.[61] Furthermore, the mean residence time of 5-FU following RT decreases in plasma and increases in bile, while the clearance reduces significantly in bile and increases significantly in plasma after RT, but no differences in the volume of distribution at steady state (Vss) between irradiated and control animals.[43,44,61]

These findings suggest that local irradiation with or without including the liver and kidneys is able to influence the AUC of 5-FU, no matter by low dose (such as off-target dose in daily practice) or by daily general dose. As mentioned above, the active metabolites of 5-FU are through anabolic pathway.[53,54] When the AUC of 5-FU is decreased by irradiation, the probability of metabolism of 5-FU through anabolic pathway may be influenced by irradiation. The interaction between irradiation and PKs of 5-FU is discovered and supports the strategy of adjuvant chemotherapy in the clinical practice.

In the lymphatic system. Little is known about the concentration of a given drug in the lymphatic system after its administration.[62] Seto and colleagues injected 5-FU through cervical vein in pigs and found that 5-FU concentrations in lymph nodes did not differ from those in plasma.[63] However, Lindner et al reported that 5-FU concentration in lower thoracic duct lymph was 5.7-fold higher than in plasma when administered via the intraperitoneal route.[64] When administered orally, 5-FU is

highly absorbable in a gastric emptying-limited manner with first-pass metabolism concerning.[65,66] In particular, intraluminal injection of 5-FU to submucosa resulted in higher levels of the drug in the colonic wall and abdominal lymph nodes in a dog model.[67] However, to the best of our knowledge, no studies have investigated the dynamic shift of 5-FU from plasma to the lymphatic system after intravenous injection. Furthermore, the biological meaning of drug concentration detected in the gross lymph nodes may differ from that detected in identifiable lymphatic vessels.

Radiation-induced increase in vascular ionizing radiation causes a dose-dependent loss in endothelial cells and hypertrophy of surviving endothelial cells,[68,69] features associated with enhanced vascular permeability that will be considered as one of the factors responsible for metastatic spread. However, it is dose dependent between 5- and 20-Gy single doses,[70] and the dose that has been shown to cause vascular disease ranges from 25 to 40 Gy.[71] Interestingly, there were no differences in the AUC of 5-FU in lymphatic fluid between animals that received local pelvic irradiation and those that did not receive irradiation.[45] These findings agreed with the results that single daily RT dose would not change the permeability of vessel or lymphatic system in delivery of 5-FU.

The RT-PK Phenomenon of CDDP

In plasma. Meta-analyses have confirmed that both platinum-based and non-platinum-based CCRT result in markedly better treatment outcomes than RT alone in patients with cervical cancer.[18,29] Nevertheless, a number of studies have found that the rates of hematological toxicities are at 2- to 10-fold greater than those who receive RT alone.[18,21-23,27-29] These analyses also revealed that the rates of serious GI toxicity were about 2-fold greater in those who have undergone CCRT than in those who have received RT alone.[21,22,27,29]

Recently, whole pelvic irradiation increased the AUC of CDDP (5 mg/kg) by 80% at 0.5 Gy and 87% at 2 Gy, which was noted in the animal study.[46] In the same study, it was found that pelvic irradiation decreased the clearance value of CDDP by 44.9% in the 0.5-Gy group and by 46.6% in the 2-Gy group. Moreover, in bile study, pelvic irradiation decreased the AUC of the CDDP by 13% at both dose levels. Intriguingly, RT also resulted in an 87% increase in AUC of the CDDP in lymphatic system at 2 Gy. Radiotherapy decreased the total plasma clearance (CL) of the CDDP in plasma by 32.0% and in the lymphatic system by 46.8%. The modulating function of pelvic RT in the RT-PK phenomenon was not only evident for 5-FU[44,45,61] but also for CDDP. In addition, both the daily dose and the off-target dose resulted in an increase in the AUC of CDDP.

Studies have demonstrated that weekly CDDP in combination with RT is equally efficacious or better and less toxic than combinations using 5-FU and/or hydroxyurea[22] or protracted venous infusion (PVI) 5-FU.[72] Furthermore, the reported frequency of transient moderate-to-severe hematologic and GI adverse effects is markedly higher in patients. Animal studies have demonstrated that local pelvic irradiation with 2 Gy results in a reduction of between 21.5% and 31.7% in the AUC of 5-FU and an increase of 87% in AUC of CDDP in rats.[43,44,46] These findings may explain, at least in part, why a platinum-based regimen concurrent with RT is a better choice than 5-FU for cervical cancer[22,73] and why PVI 5-FU is not more effective than weekly CDDP.[72] Furthermore, the RT-PK phenomenon regarding CDDP also helps to explain why CCRT is associated with a higher incidence of adverse effects than RT or chemotherapy alone.

In the lymphatic system. Platinum-based regimens administered concurrently with RT have been shown to be associated with a lower risk of locoregional failure and distant metastases than RT alone.[23,74] It has also been reported that the rate of distant failure was lower in patients who received CDDP than in those who received 5-FU via PVI (29% vs 18%).[72] As mentioned previously, a single daily RT dose does not change the permeability of vessels or the lymphatic system in delivery of 5-FU; however, 2 Gy, a practical daily dose, has been shown in rats to increase the AUC of CDDP in lymphatic fluid by 87% and to decrease the CL of CDDP in the lymphatic system by 46.8%.[46] Additionally, the AUC for CDDP was 3.4-fold greater in the lymphatic system than in plasma from rats that received RT but was 2.8-fold in rats that did not receive RT. Those findings indicate that the distribution of CDDP in the lymphatic system could be enhanced by RT.[46]

Modifying chemotherapeutic formulations in a way that increases exposure of the lymphatic system to said drugs might be an effective means of improving drug efficacy.[75] Future studies that provide a better understanding of the relationship between RT and the PK of CDDP in the lymphatic system might shed light on ways to reduce the incidence of regional and distant failure.

A Possible Mechanism Governing the RT-PK Phenomenon

Matrix metalloproteinase-8 (MMP-8), a member of the zinc-dependent interstitial collagenase subgroup of the MMP family of neutral proteinases,[76] mediates inflammatory processes.[77] The protein is expressed in response to injury in many cell types, such as neutrophils, macrophages, plasma cells, granulocytes, and epithelial choroid plexus cells.[78,79] Polymorphonuclear neutrophils (PMNs), the main source of MMP-8 in humans and mice,[80,81] degrade collagen by releasing members of the MMP family at inflammatory sites.[82]

Several stress response and cell–cell signaling molecules are believed to be involved in bystander signaling or abscopal effects. Molecules that have been proposed as participants in bystander effects include interleukin 6 (IL-6) and IL-8,[83,84] transforming growth factor-β1,[85,86] tumor necrosis factor α (TNF-α),[87] reactive oxygen species, and reactive nitrogen species.[88] Molecules that are believed to be involved in producing abscopal effects include TNF-α, IL-4, IL-18, IL-2, and granulocyte–macrophage colony-stimulating factor, cytokines that are known to be released systemically in response to

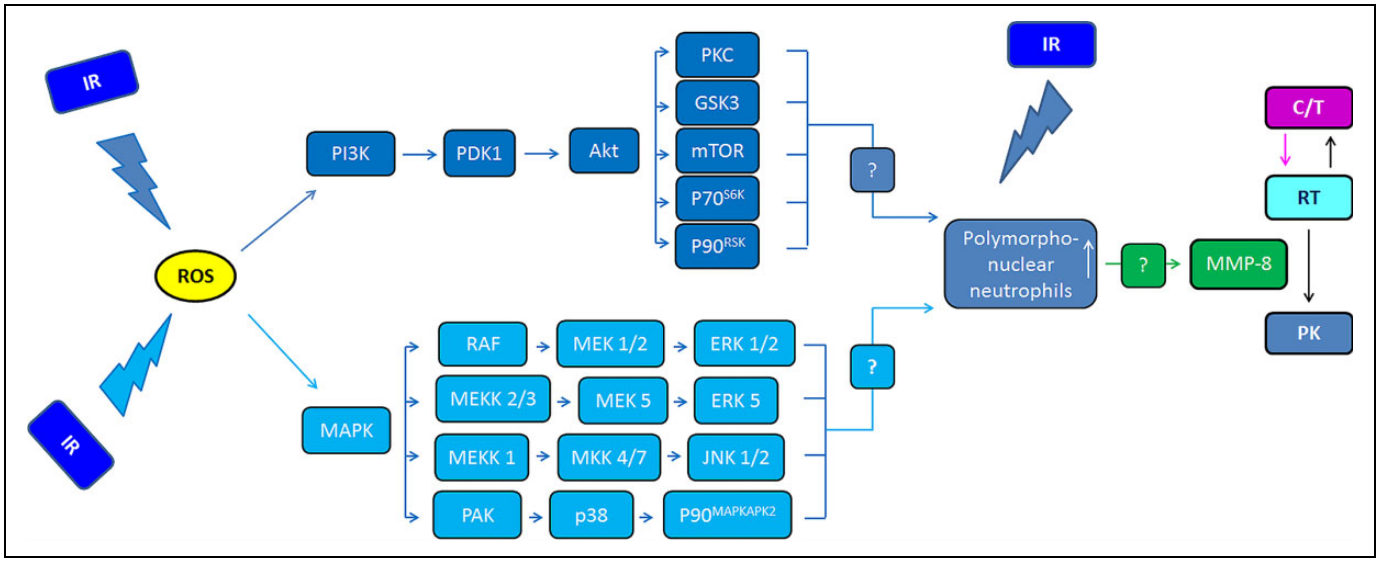

Figure 2. Possible mechanisms governing the RT-PK phenomenon. ERK indicates extracellular-regulated kinase; GSK3, glycogen synthase kinase-3; IR, ionizing radiation; JNK, c-Jun NH2-terminal kinase; MAPK, mitogen-activated protein kinase; MAPKAPK2, MAP kinase-activated protein kinase 2; MEK1/2, mitogen-activated/extracellular-regulated kinase 1/2; MEKK, mitogen-activated protein kinase kinase kinase 1; mTOR, mammalian target of rapamycin; PAK, p21-activated kinases; PDK1, serine/treonine kinase 3'-phosphoinositide-dependent kinase1; PI3 K, phosphatidylinositol 3-kinase; PKC, protein kinase C; RT-PK, radiotherapy–pharmacokinetic; ROS, reactive oxygen species; RSK, ribosomal s6 kinase.

irradiation.[89-91] Although MMP-8 has been demonstrated to play a major role in local RT-induced modulation of systemic 5-FU PK,[44] it has not been shown to correlate with bystander or abscopal effects.

Neutrophils express a large number of cell surface receptors that stimulate an inflammatory response.[92] FcγR and CR3 not only act cooperatively to initiate the actin polymerization necessary for neutrophils under stress but also activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase for O_2^- production.[93,94] Polymorphonuclear neutrophils that are exposed to appropriate stimuli activate NADPH oxidase, resulting in the generation of O_2^-.[95] Moreover, activation of phosphatidylinositol (PtdIns) 3-kinases (PI3-kinases or PI3 K) leads to the production of PtdIns(3,4,5)P3 (PIP3), and activation of protein kinase B/Akt is reported to occur after PMN stimulation and to be associated with both O_2^- production and phagocytosis.[92,96,97]

Stimulation of FcγR and CR3 also activates the p38 mitogen-activated protein kinase (MAPK) in macrophages and PMNs.[98,99] The 3 main members that integrate the MAPK family in mammalian cells are stress-activated protein kinase c-Jun NH2-terminal kinase, stress-activated protein kinase 2 (p38), and extracellular signal-regulated protein kinases 1 and 2 (p44/p42). The p38 MAPK is involved in the signaling pathway of O_2^- production.[100] Inflammatory stimuli also activate p38 MAPK, and a specific inhibitor of p38 MAPK prevents O_2^- production in PMNs that have been exposed to lipopolysaccharide and *N*-formyl-methionyl-leucyl-phenylalanine.[99,101]

Putting these observations together, it is arguable that RT induces inflammatory stress and results in the recruitment of leukocytes to the target area.[102] Neutrophils degrade collagen by releasing members of the MMP family when they are localized at inflammatory sites.[82] It promotes the secretion of MMP-8 as well as various other proinflammatory mediators to modulate the PKs of anticancer drugs. Studies have demonstrated that MMP-8 plays an important role in the RT-PK phenomenon.[44] PI3-K and p38 MAPK participate in signaling pathways governing NADPH oxidase–generated O_2^- production and phagocytosis. Therefore, it is reasonable to suspect that the MAPK family or the PI3K/Akt signaling pathway contributes to the RT-PK phenomenon. Figure 2 illustrates the possible mechanisms governing the RT-PK phenomenon.

The RT-PK Phenomena Should Be Considered in the Strategy of the Combination of Radiotherapy With Target or Immunologic Drugs or Metronomic Chemotherapy Schedule

It is an exciting time for clinical oncologists because we have undergone dramatic changes in routine practice in the last decade. These include the technological advances in radiation modalities,[47-50] the demonstration of the superiority of chemoradiotherapy over radiotherapy alone,[19,21-23,27,28,57,58,103] and the integration of novel targeted therapies or immunotherapy within standard combination strategies.[104,105]

Strategies for improving the efficacy of clinical radiotherapy focus on exploiting actionable tumor-specific molecular targets.[106] Some case reports also hint the possibility of interaction between RT and target agents.[107-109] In a phase 2 study about combined sorafenib and radiotherapy in patients with

advanced hepatocellular carcinoma, concurrent group had more grade 3 hand and foot skin reaction and diarrhea than sequential group.[110] Recently, a poster of animal study accepted by conference of ESTRO 36 confirmed there was RT-PK phenomenon also between sorafenib (target agent for hepatocellular carcinoma) and irradiation.[111]

A growing body of evidence also shows that the combination of radiotherapy with immunotherapy through abscopal responses can enhance the systemic immune response.[105,112,113] Recently, in a preclinical model, combining anti-PD-1 antibody and thoracic irradiation results in T cell infiltration into lung and heart tissue and increases mortality.[114] This observation mentions the possibility of modulation by irradiation for immunotherapy in the immune system and in the PK.

Metronomic regimens are developed to optimize the antitumor efficacy of agents that target the tumor vasculature instead of tumor cells.[14,115,116] Unlike dose-dense chemotherapy, deliver anticancer drugs with lower dose and prolonged periods of time to target tumor vasculature.[11,14] Knowledge of the preclinical PK of metronomic chemotherapies has grown slowly over the past years.[117] There are several positive results in palliative settings[118-120] or maintenance treatment.[121] Recently, data from the clinical study revealed for the first time a statistically significant relationship between the active drug PK parameters and the clinical response to the metronomic-like chemotherapy regimen.[122]

Metronomic treatment can be combined with standard chemotherapy[123,124]; antiangiogenic drugs,[125,126] antibodies targeting proteins,[127] or vascular endothelial growth factor receptor -2 and/or vascular endothelial growth factor[128,129]; anti-HER-2 antibodies[130]; immunotherapies[131,132]; or hormonal agents, such as aromatase inhibitors,[133] among others. In the clinical practice, the regular model of CCRT for RT delivering is continually multiple fractions. As we mention above, RT affects the PKs of 5-FU through MMP-8.[44] Additionally, irradiation increases the expression of endothelial interacellular adhesion molecules -1 protein[134] and increases apoptosis in microvascular endothelial cells.[135] Moreover, the endothelial sheet of vessel could be disrupt by 5-FU.[136] The data also showed the activity of MMP-8 and MMP-9 was elevated around the damaged aneurysm.[137] These findings explore the potentially modulated effects of combination of metronomic regimens and RT through RT-PK phenomena. In the future, the knowledge of interaction between the PK characteristics of metronomic regiment and RT may encounter challenges. However, it is worth to investigate the RT-PK phenomena in metronomic regimens to provide a better understanding of the optimal metronomic-dosing regimens concurrent with RT in patients, especially about the onset, intensity, duration, quality of the therapeutic effects, and reduce any harmful effects the drug might have.

Until now, we do not have a good understanding of the relationship between the maximum tolerated dose and the dose/fractionation required to achieve the desired therapeutic effect, especially for targeted agent, immunologic agents, or metronomic regimens combined with mordent radiotherapy modalities. The RT-PK phenomenon suggests that even off-target radiation doses can affect the bioavailability of the radiosensitizing drugs and that the mechanisms of these effects are multifactorial and complex in nature.[43-46,61] Our current understanding of the systemic effects of localized irradiation governed by the RT-PK phenomenon allow for the establishment of optimal RT parameters that can be incorporated into future treatment strategies.

The New Era for RT-PK Phenomena—Particle Therapy

In December 1904, William Henry Bragg and his assistant Richard Kleeman published "On the ionization of curves of radium" in the Philosophical Magazine (London), named the Bragg-peak, that gave measurements of the ionization produced in air by alpha particles and noted a particle is a more efficient ionizer toward the extreme end of its course. In front of the Bragg-peak, the dose level is modest as compared to photon beams; beyond this peak, no further dose deposition occurs.[138] In the mid-1940s, Robert Wilson hypothesized that highly localized deposition of energy from proton beams could increase the radiation doses to tumors and minimize radiation to adjacent normal tissues. Shortly thereafter, scientists at the Lawrence Berkeley Laboratory initiated the first studies on proton irradiation to confirm this hypothesis.[139]

Conventional cancer radiation therapy uses several types of ionizing radiation (X-rays, gamma rays, or electron beams) to treat tumors. Ionizing radiation damages the DNA of tumor and healthy cells alike, triggering complex biochemical reactions and eventually resulting in cell death. Charged particles such as protons have little exit dose beyond the target volume, thereby greatly sparing adjacent normal tissues. The dosimetric advantages of protons have been demonstrated in numerous planning studies compared to 3DCRT and IMRT.[140,141] Additionally, the newly developed intensity-modulated proton therapy has been shown to yield superior dose distributions to photon IMRT, with the added advantage of a significant reduction in the volume of healthy normal tissues exposed to low-to-medium doses.[142,143] These physical characteristic allows proton beam therapy to improve the therapeutic ratio by limiting toxicities while at the same time delivering higher radiation doses.

The biological effects of proton beams were similar to conventional radiations used in radiotherapy. The relative biological effectiveness of protons suitable for large-field radiotherapy, compared with ^{60}Co gamma rays, is generally in the range 1.0 to 1.25 and remains the same with depth of penetration, except for the descending portion of the depth–dose curve. The oxygen enhancement ratio for high-energy protons is not significantly different from that of X-rays.[144] The above discussion assumes that the sole difference between photon and proton irradiation is the physical dose distribution and that the biological effect per dose could be equivalent.

As mentioned previously, even off-target radiation doses can modulate the bioavailability of the radiosensitizing

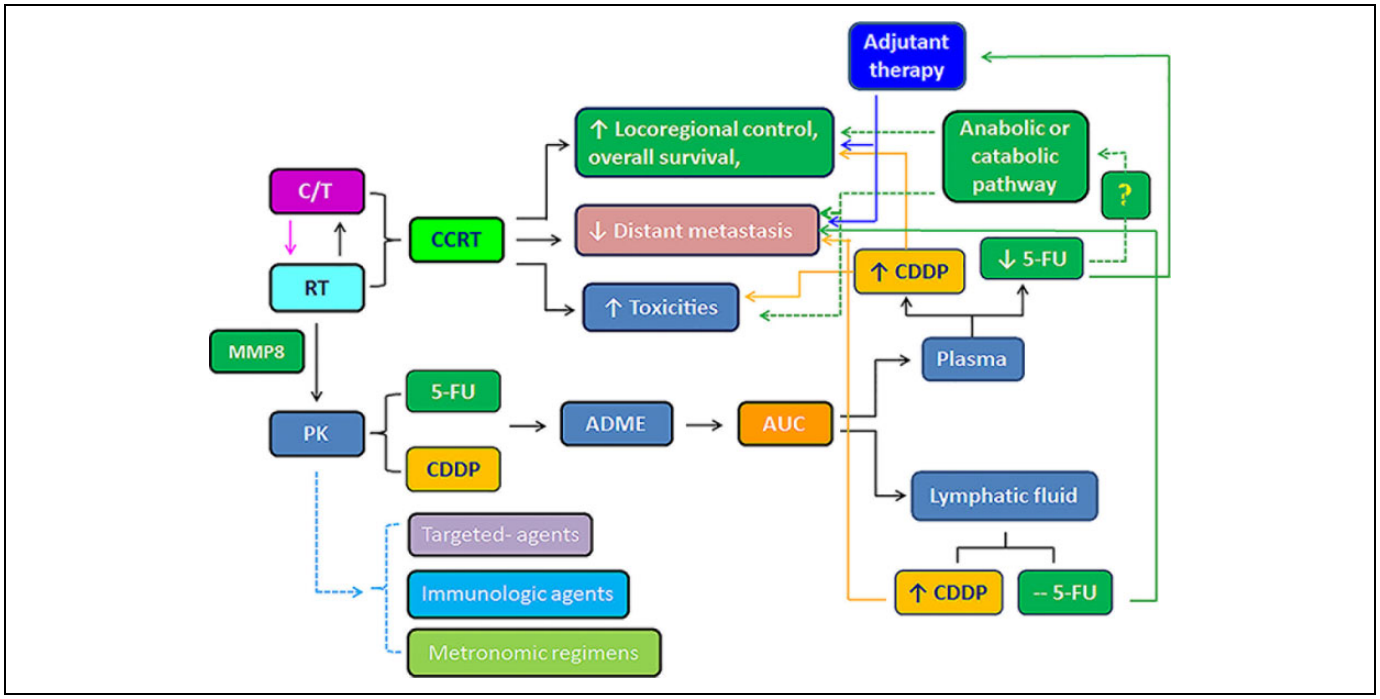

Figure 3. Diagram of the RT-PK phenomenon. The dotted arrow line indicates that more evidence is needed to establish a correlation. The solid arrow line indicates correlation. "–" indicates irradiation does not modulate the pharmacokinetics; "↑," increment; "↓," decrease; 5-FU, fluorouracil; ADME, absorption, distribution, metabolism, excretion; CDDP, cisplatin; C/T, chemotherapy; CCRT, concurrent chemoradiation therapy; MMP-8, matrix metalloproteinase-8; PK, pharmacokinetic; RT, radiotherapy.

drugs.[43-46,61] Interestingly, proton beams therapy has Bragg-peak phenomena.[138] Notably, the biological effects of proton beams are similar to the conventional radiotherapy. This characteristic of proton beam makes irradiation doses delivering with restricted off-target doses to the surrounding tissue at the same time. It could be expected the RT-PK phenomenon persists between proton beam therapy and anticancer agents. Additionally, it is also worth to look forward to the possible different expressions of PK between photon and particle therapy.

Conclusion

The RT-PK phenomenon provides a clue to understanding the unexplained biological enhancement of antineoplastic agents. Both targeted and off-target RT affect the systemic PK of antineoplastic agents as seen in Figure 3. Further elucidation of the RT-PK phenomenon of antineoplastic agents will give us the opportunity to expand the scope of radiation oncology. It will also allow for the development of new radiation-modulated strategies that do not subject patients to severe toxicity.

Authors' Note

Y. J. Chen and T. H. Tsai contributed to the design and analysis of the work. C. H. Hsieh drafted the manuscript and designed the work. L.Y. Wang gave advice on the work. Y.J. Chen, T.H. Tsai, and L.Y. Wang involved in revising the manuscript. All authors read and approved the final manuscript. Yu-Jen Chen and Tung-Hu Tsai contributed equally to the study.

Declaration of Conflicting Interests

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